A Short Enantioselective Total Synthesis of (–)-Linderol A

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Abstract: An efficient short enantioselective total synthesis of (–)-linderol A was achieved via a five-step reaction with 30% overall yield, starting from 4-methoxyphloroacetophenone.

Key words: total synthesis, stereoselectivity, terpenylation, epoxides, hexahydrodibenzofuran

(–)-Linderol A [(–)-**1**, Figure 1], a monoterpene-substituted chalcone with four successive asymmetric carbons at the 6 (*R*), 5a (*R*), 9a (*S*) and 9 (*R*) positions, was isolated in 1995 from the fresh bark of *Lindera umbellata* (Lauraceae) by Sashida and co-workers.[1] They also reported the potent inhibitory activity of this natural product on the melanin biosynthesis of B-16 melanoma cells without causing any cytotoxicity on the cultured cells.[1]

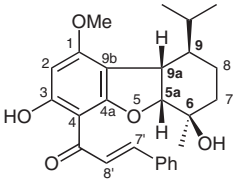


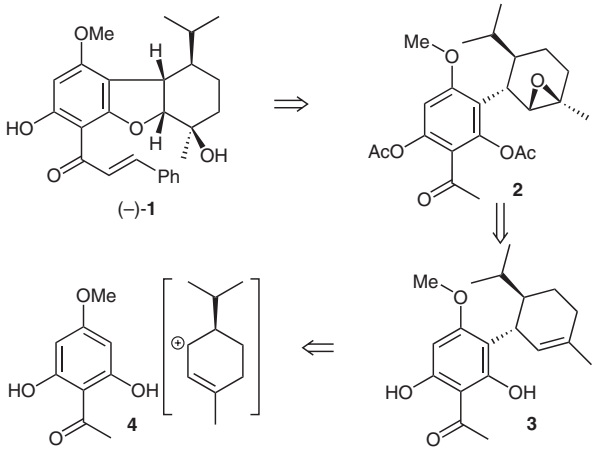
Figure 1 Structure of (–)-linderol A [(–)-**1**]

Its first total synthesis in racemic series was reported by Ohta and co-workers.[2] The critical step of their strategy was a tandem reaction of a 3-ethoxycarbonylcoumarin derivative with dimethylsulfoxonium methylide to give the 2-ethoxycarbonylcyclopenta[*b*]benzofuran-3-ol derivative. Further they applied a stereoconvergent approach to dibenzofuran derivatives from benzo[*b*]cyclobuta[*d*]pyran derivatives to the second-generation synthesis of (±)-linderol A.[3]

Although they considerably improved the synthetic route to linderol A by decreasing the number of steps from twenty to twelve and increasing the overall yield from 7.64% to 25%, to the best of our knowledge, no asymmetric synthesis of (–)-linderol A has ever been described.

To fulfill this goal, we envisaged the total synthesis of the optically active natural product in a minimum of steps, starting from an easily available commercial reagent. Our retrosynthetic approach is outlined in Scheme 1. The hexahydrodibenzofuran ring can be obtained from a stereospecific intramolecular epoxide opening with phenolate anion (via ester hydrolysis of **2**) before the introduction of the chalcone chain.

The endocyclic epoxide **2** could be formed from acetylated **3** using an epoxidation that would be diastereoselective because of the steric bulk on the adjacent side of the alkene. Furthermore, the first key step of our strategy is a terpenylation of 4-methoxyphloroacetophenone (**4**) with an allylic cation generated from the suitable chiral monoterpene (–)-α-phellandrene.



Scheme 1 Retrosynthetic approach

Terpenylation using (–)-α-phellandrene was previously described by Crombie and co-workers for the synthesis of (3*S*,4*R*)-(+)-linderatin, a monoterpenylated dihydrochalcone.[4] The procedure was slightly modified for our reagent (Scheme 2): treatment of 4-methoxyphloroacetophenone (**4**)[5] with (–)-α-phellandrene in the presence of *p*-toluenesulfonic acid in toluene at room temperature for one hour gave the monoterpenylated compound **3** in 76% yield after silica gel column chromatography. As expected, the relative configuration between H3 and H4 is *trans* (confirmed by ^{1}H NMR data: $J_{3,4}$ = 8.8 Hz).

The corresponding diacetate product **5** was prepared in good yield from **3** by acetylation in pyridine at 70 °C for 24 hours. Compound **5** was characterized by its spectroscopic data (NMR and MS) and its optical rotation was also determined.[6]

To finalize our synthesis, we have been inspired by the works developed by Razdan et al. to build the chosen tricyclic system with control of asymmetric centers (see Scheme 3).[7] Diacetate compound **5** was allowed to react

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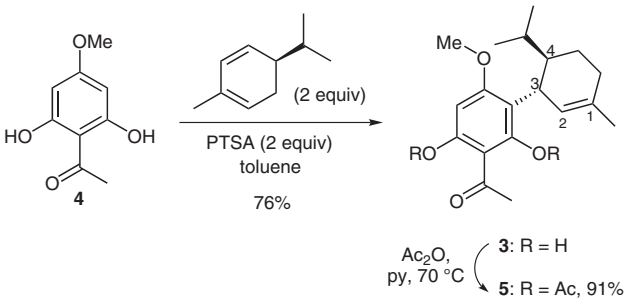
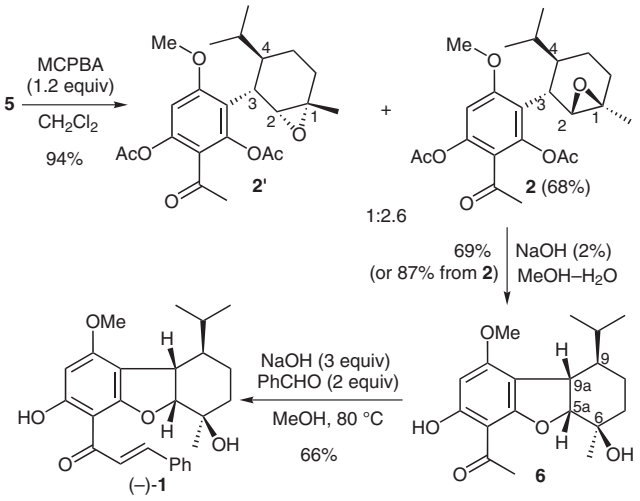


Scheme 2 Terpenylation reaction

at room temperature with *m*-chloroperbenzoic acid in methylene chloride for 1 hour, giving a mixture of the two diastereomeric epoxides **2** and **2′** (94%), favoring the desired compound **2** in a ratio of 2.6:1 (evaluated by ^{1}H NMR spectrum). According to this diastereomeric ratio, the yield for **2** is actually 68%. Epoxidation of **5** occurs preferentially on the less substituted face; the low selectivity can be explained by the presence of the isopropyl group on the same face.

The nature of endocyclic epoxides (**2** and **2′**) was correlated on the basis of the ^{1}H NMR spectra: at δ = 3.07 and 3.61 ppm (d, 1 H, J = 10.7 Hz, C3H) and at δ = 2.82 and 2.92 ppm (s, 1 H, C2H). These data were in agreement with the literature.[7]



Scheme 3 Ring closure via epoxide opening

The unseparated epoxides **2** and **2′**, in the presence of 2% sodium hydroxide in methanol–water (1:1) at room temperature for one hour, led in good yields to the hexahydrodibenzofuran derivative **6** after deacetylation and resulting phenolate attack on the oxirane.

The transformation of **2** to **6** involves an intramolecular *trans* opening of the epoxide at the less hindered site, fixing the relative stereochemistry of the fused furan ring at C5a and C9a protons as *cis*. The configuration of the C6 quaternary carbon bearing the hydroxyl group is *R*. Compound **6** was fully characterized by its spectroscopic data (IR, NMR, and MS).[8] The two bridgehead hydrogens exhibited a $^3J_{5a,9a}$ coupling constant of 5.5 Hz suggesting coplanarity.

Considering epoxide **2′** as a nonproductive starting material for ring opening, the exact yield is 87% starting from **2** (see Scheme 3).

(–)-Linderol A was finally obtained after introduction of the chalcone side chain by treatment of **6** with benzaldehyde in the presence of NaOH in methanol at 80 °C (66%).

The spectroscopic properties of the synthetic (–)-**1** (NMR and MS) were identical to those previously reported[1,2] and the optical rotation ($[\alpha]_D$ –27, c = 0.833, $CHCl_3$) was in agreement with that reported for the natural compound {$[\alpha]_D$ –22.7 ($CHCl_3$; no precise concentration given in the literature)}.[1]

Yamashita et al. have confirmed the absolute configuration of (–)-**1** after racemic resolution and found –32.8 (c 1.0, $CHCl_3$) as the specific rotation.[9]

In conclusion, we have completed the first enantioselective total synthesis of (–)-linderol A after five steps in 30% overall yield. Two key reactions have been used, terpenylation and a stereospecific intramolecular epoxide opening with a phenolate anion.

Improvement of each reaction step, and especially the asymmetric epoxidation, is currently under investigation in order to optimize our synthesis.

Acknowledgment

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(6) **Selected Physical Properties for 5**
$[\alpha]_D$ +14 (c 0.44, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.56 (s, 1 H, H_{ar}), 5.09 (s, 1 H, H2), 3.80 (m, 4 H, H3 and CH_3O), 2.40 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3), 2.03 (m, 2 H), 1.90 (m, 1 H), 1.78 (dt, 1 H, J = 2.3 Hz), 1.63 (s, 3 H, CH_3), 1.36 (m, 2 H), 0.86 (d, 3 H, J = 6.8 Hz,

CH_3), 0.77 (d, 3 H, J = 6.8 Hz, CH_3) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 198.4 (C=O), 169.2 (C=O), 168.5 (C=O), 160.1 (Cq), 147.4 (Cq), 147.1 (Cq), 132.9 (Cq, C1), 124.9 (CH, C2), 124.3 (Cq), 102.6 (CH_{ar}), 55.9 (CH_3O), 42.5 (CH), 36.0 (CH, C3), 30.8 (CH_3), 30.6 (CH_2), 28.0 (CH, C4), 23.4 (CH_3), 22.3 (CH_2), 21.5 (CH_3), 21.1 (CH_3), 20.8 (CH_3), 15.9 (CH_3) ppm. LRMS (EI): *m/z* (%) = 402 (0.1) [M^+], 359(52), 317(99), 290(22), 248(100), 233(30). HRMS (EI): *m/z* calcd for $C_{23}H_{30}O_6$: 402.2042; found: 402.2041.

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(8) **Experimental Procedure for 6**
The mixture of epoxides **2** and **2′** (52.8 mg, 0.126 mmol with a ratio of 2.6:1) was treated at r.t. with 2 mL of a 2% NaOH solution in MeOH–H_2O (1:1). The solution was stirred at r.t. for 1 h, then neutralized with 10% HCl. The mixture was extracted with CH_2Cl_2, the organic layer was washed with H_2O and dried over $MgSO_4$. The solvent was then removed under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2–EtOAc, 90:10) to give **6** as a pale yellow solid (29 mg, 0.087 mmol, 69% or 87% from **2**); mp 146–147 °C. IR (KBr): 3430, 2947, 2921, 1625, 1433, 1363, 1293, 1211, 1150, 1054, 831, 805 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 13.16 (s, 1 H, OH), 6.02 (s, 1 H, H2), 4.16 (dd, 1 H, J = 5.5, J = 1.0 Hz, H5a), 3.81 (s, 3 H, CH_3O), 3.11 (dd, 1 H, J = 11.1, 5.5 Hz, H9a), 2.60 (s, 3 H, CH_3), 1.80 (m, 3 H, H7 and $CH_{i\text{-}Pr}$), 1.61 (s, 1 H, OH), 1.50 (s, 3 H, CH_3), 1.40 (m, 2 H, H8), 1.10 (m, 1 H, H9), 0.90 (d, 3 H, J = 6.9 Hz, CH_3), 0.83 (d, 3 H, J = 6.9 Hz, CH_3) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 201.8 (C=O), 165.0 (C3), 162.0 (Cq_{ar}), 161.8 (Cq_{ar}), 113.1 (C9b), 102.9 (C4), 92.5 (C2), 92.3 (C5a), 69.3 (CH, C6), 55.4 (CH_3O), 46.5 (CH, C9), 39.6 (C9a), 35.2 (CH_2, C7), 31.1 (CH_3C=O), 28.2 (CH_3), 27.1 ($CH_{i\text{-}Pr}$), 21.7 (CH_3), 17.1 (C8), 15.3 (CH_3). LRMS (EI): *m/z* (%) = 334 (50) [M^+], 318 (40), 249 (98), 233 (100), 207 (48), 195 (22). HRMS (EI): *m/z* calcd for $C_{19}H_{26}O_5$: 334.1780; found: 334.1788.

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